M E M O R A N D U M **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: September 24, 2002

FROM: Thomas P. Laughren, M.D.
Team Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: November 4, 2002 Meeting of Psychopharmacological Drugs Advisory Committee (PDAC) on the InterSePT Study (Study ABA 451)

TO: Members of PDAC

As you know, the PDAC will be meeting on November 4th to discuss the findings and regulatory implications for the InterSePT Study (Study ABA 451), a study that compared clozapine and olanzapine on the outcome of emergent suicidal behavior and thinking in schizophrenic and schizoaffective patients who were judged to be at risk of suicide.

Novartis Pharmaceuticals, the sponsor for Clozaril (clozapine), submitted supplemental application NDA 19-758/S-047 on February 28, 2002 in support of a new claim for the use of Clozaril for the treatment of suicidality in patients with schizophrenia or schizoaffective disorder. After reviewing this application, FDA issued an approvable letter on August 30, 2002, based on our view that the results from this study, along with other data from the "ERI Study," a cohort mortality based on findings from the Clozaril registry, could support a new claim for Clozaril in reducing the risk of emergent suicidal behavior in schizophrenic and schizoaffective patients who are judged to be at risk for emergent suicidal behavior, based on history and recent clinical state.

While we have reached a preliminary conclusion that, on face, the results from this trial might support this new claim, there remain questions and issues that need to be resolved prior to our taking a final action on this application. These questions and issues are of sufficient importance that we felt it would be useful to bring this application to the PDAC for independent feedback prior to our taking a final action. While there are a number of questions and issues that may benefit from such feedback, the following two issues are of particular importance, in our view. These issues are discussed in detail in the various documents that we have included in FDA's package for this meeting, thus, we will identify these key issues only briefly in this memo, as follows:

1. There are several matters relating to the InterSePT Study, in regard to its design and conduct. We feel that most critical of the various questions regarding this study is the matter of potential bias in the referral of events to the Suicide Monitoring Board (SMB) for confirmation as Type 1 events. As noted in our reviews and memos, we feel that the unblinded nature of the study raises the possibility that knowledge of treatment assignment

might have produced a bias in favor of clozapine with regard to the referral of events to the SMB. FDA is currently engaged in a specific audit of clinical records at a sample of study sites to try to address this concern, and we hope to have the results of this audit available to present to the committee in time for the November 4, 2002 meeting.

2. The second issue is the new claim being proposed. There is no precedent for an indication focusing on suicidal behavior, and we seek the committee's feedback both on the general question of whether or not suicidal behavior in schizophrenia and schizoaffective disorder is an appropriate target for a claim, and also the specific claim being sought by Novartis in this supplemental application. Novartis had originally sought a claim for "the treatment of suicidality in patients with schizophrenia or schizoaffective disorder....." Alternatively, we have proposed in our draft of labeling that the claim be for "reducing the risk of emergent suicidal behavior in patients with schizophrenia or schizoaffective disorder who are judged to be at risk for emergent suicidal behavior....." We request the committee's feedback on this more specific question, as well the following important related questions about the nature of the claim:

-Clozaril is currently limited in its approved indication to refractory schizophrenia, i.e., it is not indicated for either nonrefractory schizophrenia or schizoaffective disorder. Do these data support an extension of the claim for suicidal behavior into these additional populations?

-How should the trial be interpreted with regard to olanzapine, the active control in the InterSePT Study? Should Clozaril be considered to be superior only to olanzapine with regard to suicidality, or superior in general to other antipsychotic drugs, and how should this superiority be characterized in labeling? Alternatively, does the Committee believe that olanzapine was utilized at maximally beneficial doses; if not, can any fair comparison to olanzapine be made (i.e., does the study only support a non-comparative conclusion that clozapine reduces the risk of suicidality)?

-The sponsor has submitted the results of a single randomized controlled trial that purports to demonstrate the effectiveness of clozapine in reducing the risk of suicidality. Ordinarily, of course, at least two adequate and well-controlled trials are required, however, effectiveness can also be established on the basis of a single well-controlled trial and "confirmatory evidence". While not typically employed, this standard may be used in those cases in which the single trial documents an effect on mortality or irreversible morbidity, which would make replication difficult. In addition, this standard may also be employed when the single study is very strongly positive (i.e., the p-value for the between-treatment contrast is very small), individual centers are "positive", results are internally consistent (e.g., the drug effect is similar in various severity strata), etc. We are interested to know if the Committee believes that the data in this application meet this alternative standard.

In this regard, it is important to note that the sponsor has not presented any affirmative evidence that clozapine actually has an effect on preventing suicide. Given this, we must ask if the finding seen on the outcome "suicidality" as defined in the trial is sufficiently

persuasive to base approval on this single prospective controlled controlled trial and the auxiliary information provided.

There are, of course, other questions and issues of interest, some of which FDA staff may raise at the meeting, but committee members are also encouraged to raise issues of concern to them about this study and the regulatory implications.

The general question for which we will be wanting a committee vote pertains, of course, to whether or not the data support a new claim for Clozaril regarding suicidal behavior. Since the exact nature of that claim is also a key issue for discussion, it is difficult to articulate the exact question in advance of the meeting. Therefore, part of the committee's task will be to articulate the precise question on which it will then need to vote.

FDA's package for the committee will include the following:

-FDA's August 30, 2002 approvable letter for this application, including our draft labeling

-The primary medical officer review of this application by Gregory Dubitsky, M.D.

-An amendment by Dr. Dubitsky to his original review, focusing on new data pertinent to the validity of SMB classifications of potential Type 1 events by the SMB

-The primary statistical review of this application by Kun He, Ph.D.

-The team leader memo for this application by Thomas Laughren, M.D.

-The division director memo for this application by Russell Katz, M.D.

We look forward to seeing you on November 4th, and thank you in advance for all of your efforts in helping us deal with this complex issue.

cc:
Orig NDA 19-758
HFD-120
HFD-120/TLaughren/RKatz/GDubitsky/SHardeman
HFD-101/RTemple
HFD-021/STitus

DOC: CLOZPDAC.DOC

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Thomas Laughren
9/24/02 01:42:10 PM
MEDICAL OFFICER